

819-4

### Obesity Predicts Coronary Endothelial Dysfunction Independently of Inflammation, Atherosclerosis, and Conventional Risk Factors

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**Background:** Obesity is a well recognized modifiable risk factor for coronary artery disease (CAD) that is associated with insulin resistance, dyslipidemia, hypertension and low-grade inflammation. We investigated the relationship between coronary vascular endothelial dysfunction, obesity and its metabolic correlates.

**Methods:** Coronary vascular function testing was performed in 418 patients (203 with normal coronary arteries). Change in coronary blood flow (dCBF) was measured using a Doppler flowire during intra-coronary acetylcholine (15mg/min), and adenosine (2.2mg/min) infusion to test endothelium-dependent, and -independent coronary microvascular function. Patients were grouped according to body mass index (BMI); group 1 (<25kg/m<sup>2</sup>, n=90), group 2 (25-30kg/m<sup>2</sup>, n=163), group 3 (>30kg/m<sup>2</sup>, n=164).

**Results:** Prevalence of diabetes and hypertension, as well as total cholesterol, low density lipoprotein, and triglyceride levels were increased, whereas high density lipoprotein was lower with increasing BMI. C-reactive protein (CRP) was elevated in group 3 compared with 1 and 2 (1.15±0.73 Versus 0.74±0.67 and 0.74±0.57mg/dl respectively, p<0.001). During acetylcholine administration, dCBF was reduced with increasing BMI (135±102, 104±101, and 95±88% in groups 1-3 respectively, p=0.009), whereas dCBF was similar during adenosine infusion (377±152, 363±173, and 358±186% in groups 1-3 respectively p=0.67). The association between BMI group and dCBF with acetylcholine was independent of CAD and its risk factors, including CRP, by multivariable analysis (p<0.05). Furthermore, reduced dCBF with acetylcholine was also observed in the cohort of obese subjects with normal coronary arteries (135±95, Versus 102±84% in groups 1 and 3 respectively, p=0.01).

**Conclusion:** The relationship between obesity and coronary vascular endothelial dysfunction remains independent of the associated adverse CAD risk factor profile. Thus, weight loss may improve CAD risk over and above the observed benefits on conventional risk factors.

2:45 p.m.

phy in 10 patients with CHF (New York Heart Association Class II-IV) during intra-brachial infusion of 1400W (0.1-1 µmol/min), N<sup>G</sup>-monomethyl-L-arginine (L-NMMA, a non-selective NOS inhibitor; 2-8 µmol/min) and norepinephrine (as a control vasoconstrictor; 60-480 pmol/min).

**Results:** There were no changes in heart rate, mean arterial pressure or non-infused forearm blood flow during drug infusions. Intra-brachial infusion of L-NMMA and norepinephrine caused dose dependent reductions in infused forearm blood flow (p<0.05 for both); peak reductions of 28±4% and 48±6% respectively. In contrast, 1400W had no effect on blood flow: -2±3% change with 1400W at 1 µmol/min (95% confidence intervals, -7 to 3%, p=ns).

**Conclusion:** In contrast to earlier reports, we have found that selective iNOS inhibition does not affect forearm blood flow in patients with CHF. These findings suggest that the effects on vascular tone seen after administration of poorly selective NOS inhibitors may be largely due to inhibition of eNOS. Inducible NOS activity does not appear to contribute to the maintenance of peripheral vascular tone in patients with symptomatic CHF.

## ORAL CONTRIBUTIONS

820

### Metabolic Syndrome and Atherogenic Dyslipidemia

Monday, March 08, 2004, 2:00 p.m.-3:30 p.m.  
Morial Convention Center, Room 217

2:00 p.m.

820-1

### Comparative Effects of Statins on Atherogenic Dyslipidemia in Patients With the Metabolic Syndrome

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**Background:** Atherogenic dyslipidemia is a major modifiable aspect of the metabolic syndrome. We assessed the effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin on lipids in adult hypercholesterolemic (low-density lipoprotein cholesterol [LDL-C] ≥160 mg/dL and <250 mg/dL; triglycerides [TG] <400 mg/dL) patients with the metabolic syndrome.

**Methods:** These patients from the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial (4522L/0065) met ≥3 of 5 of the National Cholesterol Education Program metabolic syndrome criteria, with body mass index >30 kg/m<sup>2</sup> substituted for the waist circumference criterion. Treatments for 6 weeks were rosuvastatin 10, 20, or 40 mg, atorvastatin 10, 20, 40, or 80 mg, simvastatin 10, 20, 40, or 80 mg, or pravastatin 10, 20, or 40 mg. Rosuvastatin was compared statistically with equivalent or higher doses of the comparators (significance level adjusted to account for multiple comparisons).

**Results:** Out of 2268 patients, 811 met these criteria. Mean baseline values were 190 mg/dL for LDL-C and 215 mg/dL for TG. Reductions from baseline were 44-55%, 37-50%, 28-47%, and 20-29% for LDL-C, and 22-34%, 23-33%, 15-23%, and 12-15% for TG, with rosuvastatin, atorvastatin, simvastatin, and pravastatin, respectively. The table shows high-density lipoprotein (HDL)-C and non-HDL-C.

Overall baselines and least-square mean % changes from baseline in non-HDL-C and HDL-C

	Rosuvastatin (n=49-61/group)		Atorvastatin (n=48-65/group)		Simvastatin (n=49-62/group)		Pravastatin (n=58-69/group)	
	Non-HDL-C	HDL-C	Non-HDL-C	HDL-C	Non-HDL-C	HDL-C	Non-HDL-C	HDL-C
Baseline, mg/dL	234	45	234	44	231	44	231	44
10 mg	-40	+7.6	-34	+7.2	-26 <sup>a</sup>	+8.3	-19 <sup>a</sup>	+3.3
20 mg	-48	+11.1	-38 <sup>b</sup>	+9.4	-35 <sup>b</sup>	+9.5	-21 <sup>ab</sup>	+6.9
40 mg	-52	+10.4	-46	+5.0	-36 <sup>bc</sup>	+8.0	-27 <sup>abc</sup>	+6.4
80 mg			-46	+4.7 <sup>b</sup>	-42 <sup>c</sup>	+10.0		

Significantly different (p<.002) compared with <sup>(a)</sup>rosuvastatin 10 mg, <sup>(b)</sup>rosuvastatin 20 mg, <sup>(c)</sup>rosuvastatin 40 mg

**Conclusion:** Rosuvastatin had the most favorable effect on the atherogenic dyslipidemia associated with the metabolic syndrome.

819-5

### Atorvastatin Restores Endothelial Function in Normocholesterolemic Smokers

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Cigarette smoking impairs endothelial function and is a major cause of atherosclerosis. Research suggests that statins benefit vascular function independent of their lipid lowering effects. We hypothesized that statin therapy would improve endothelial function in normocholesterolemic smokers. We performed a randomized, double-blind, crossover, placebo-controlled study of atorvastatin (Atorva), 40 mg daily, in 20 smokers (S) and 20 healthy subjects (H). Subjects had vascular function testing and skin biopsy after each 30 day treatment. Ultrasonography was used to measure brachial artery flow-mediated, endothelium-dependent vasodilation (EDV) and nitroglycerin-induced (0.4 mg) endothelium-independent vasodilation (EIV). To determine mechanisms of the findings skin endothelial NO synthase (eNOS) mRNA expression was assessed by RT-PCR and normalized to GAPDH. Skin nitrotyrosine concentration, an intracellular marker of oxidative stress, was determined via enzyme immunoassay. The mean age (42 vs. 38 y), total cholesterol (188 vs. 176 mg/dL), LDL (103 vs. 95 mg/dL), and HDL (54 vs. 54 mg/dL) (all p>0.1) were similar in S and H, respectively. EDV was less in S compared with H (8.0% vs. 12.1%, p = .003), but there was no difference in EIV (18.6% vs. 21.0%, p = .34). Atorva restored EDV in S (8.0% to 10.5%, p = .017), but had no effect in H (12.1% to 11.0%, p = .37). Atorva did not affect EIV in either group. Atorva decreased total and LDL cholesterol in both groups, but there was no relationship between the change in total or LDL cholesterol and EDV. Skin eNOS mRNA was higher in S than H (.77 vs. .56, p = .04), suggesting that eNOS content was not responsible for impaired EDV in S. Atorva increased eNOS content in H (.56 vs. .62, p = .026), but not in S (.77 vs. .77, p = .95). Nitrotyrosine concentration was higher in S than H (82.4 vs. 38.1, p = .05), indicative of increased oxidative stress, but did not change with Atorva. Conclusion: Atorva restores endothelial function in normocholesterolemic smokers, independent of LDL lowering. Improved NO bioavailability with statin, may result from eNOS activity changes, since it cannot be ascribed to changes in eNOS content or reduction in oxidative stress.

3:15 p.m.

819-6

### Inducible Nitric Oxide Synthase Activity Does Not Contribute to the Maintenance of Peripheral Vascular Tone in Patients With Symptomatic Congestive Heart Failure

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**Background:** There have been previous reports of inducible nitric oxide synthase (iNOS) activity in the peripheral vasculature of patients with symptomatic congestive heart failure (CHF). However, these studies used the poorly selective inhibitor, aminoguanidine, which has considerable action on endothelial nitric oxide synthase (eNOS). For the first time, we have used the highly selective iNOS inhibitor, 1400W, (~10,000-fold more selective for iNOS than for eNOS) to determine whether iNOS activity contributes to the maintenance of vascular tone in patients with symptomatic CHF.

**Methods:** Bilateral forearm blood flow was recorded using strain-gauge plethysmogra-